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Workshop Summary

Relating inflammatory changes in asthma to clinical status

J. BOUSQUET

Hôpital Arnaud de Villeneuve, Montpellier, France

The biological basis of chronic airway inflammation and the effect of drugs on the inflammatory process have been well characterized, as discussed in some of the papers in this supplement (1–3). Nevertheless, the correlation of changes in inflammatory mediators and cells with changes in clinical status requires clarification. Long-term studies are also needed to determine whether changes in markers of airway remodelling are reflected in altered disease progression and clinical outcome.

Reduction of bronchial inflammation appears to improve lung function (4,5), although the exact mechanism is still debatable. Furthermore, reduction of immunological reactivity in the bronchial wall has been shown to reduce bronchial hyperresponsiveness (6), but whether it can also reduce predisposition to allergic reactivity has yet to be established. Although reductions in inflammatory markers observed in bronchial biopsy or other studies may be significant at the biochemical or histological level, they may not always correlate with changes in clinical endpoints. The reciprocal of this may also hold true; in a recent study in mild and moderate asthma patients, 4 weeks' treatment with an inhaled corticosteroid improved forced expiratory volume in 1 sec (FEV_1) and peak expiratory flow but did not produce large reductions in inflammatory markers (7). This poor correlation may be due to the large time difference between the alteration in cell numbers or levels of inflammatory markers and improvement in clinical symptoms (4). An alternative explanation is that the clinical presentation of asthma depends on the interplay of a very large number of cellular and molecular processes, which may be quite different in individual patients.

Although studies investigate the effects of asthma therapy at several different levels, i.e. clinical, physiological, immunological, cellular, molecular and genetic, the degree of response to treatment at each level varies considerably. As the level of measurement becomes more detailed, its influence on the clinical phenotype falls. For example, a change in a physiological measurement such as FEV_1 is usually a major determinant ($\geq$50%) of the total clinical presentation, but at the other extreme, the same degree of change in levels of a particular cytokine may make only a 2–5% contribution to the clinical phenotype. Although it is important to know exactly what happens at each level of measurement when treating asthma patients, the correlation between the effects of a drug on a specific inflammatory marker and on the clinical status of the patient will be limited, or at best variable.

A consensus was reached by the workshop delegates on the assessment criteria (biopsy and other) that should be selected to confirm whether a drug has anti-inflammatory activity. The two major elements of bronchial inflammation that should be evaluated are cellular inflammation and structural changes. In addition, bronchial hyperreactivity (BHR) should be measured, as it may reflect changes in both the other elements. Monitoring the number or severity of acute exacerbations is another clinical measure which should correlate with inflammatory changes.

Reductions in the numbers of T cells, eosinophils and macrophages in biopsy samples or in bronchoalveolar lavage (BAL) should be monitored using immunohistochemistry. Delegates also supported the use of markers of cell activation, for example eotaxin and the expression of its specific receptor, CCR3, for eosinophils (8). Better tools are required to analyse gene expression and protein synthesis in biopsies. In addition to cell numbers, cell function should be determined, e.g. degranulation of eosinophils and mast cells. An improvement in the reproducibility of cell function assays is required to allow better monitoring of the role of cells in the inflammatory process.

The delegates also agreed that measuring the volume of the airway sub-mucosa, either by biopsy or computerized tomography, would allow mucosal oedema or increase in muscle mass to be monitored. Mucosal oedema can be quantified by measuring changes in the vascular permeability to proteins such as albumin or α_2-macroglobulin (9,10). Other changes to bronchial vasculature, such as the density or number of blood vessels in the mucosa can be measured as described in this supplement (1). The epithelium and the basement membrane (BM) are important structural elements of the airway that should be assessed. Restoration of epithelial integrity and reduction in the amount of matrix proteins in the BM, such as collagen and tenascin, may be detected using electron microscopy; the production of tenascin may be useful as a surrogate marker of BM thickness (11), although the relevance of this marker has yet to be determined. The surface of the bronchial mucosa may be visually examined during

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Correspondence should be addressed to: Prof. Jean Bousquet, Services des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France. E-mail: jean.bousquet@wanadoo.fr

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bronchoscopy to determine any changes in the macroscopic signs of inflammation.

In conclusion, bronchial biopsy is a powerful tool that we can use to directly measure inflammation in airway tissues. Other techniques for sampling luminal contents and secretions, such as BAL and induced sputum, can complement the information obtained from biopsies, from which more can be learned about the underlying mechanisms of the acute and chronic processes. In addition, inclusion of biopsy assessments in clinical trials, particularly when the challenges posed by study design are overcome, will help us to understand more fully the activity profiles of the drugs that we use to treat asthma patients, and to assess the potential of promising new anti-inflammatory therapies in development.

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